

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/38, 31/54, 31/41</b>		A2	(11) International Publication Number: <b>WO 97/30704</b>
			(43) International Publication Date: <b>28 August 1997 (28.08.97)</b>
(21) International Application Number: <b>PCT/US97/02874</b>		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: <b>25 February 1997 (25.02.97)</b>			
(30) Priority Data: <b>60/012,250 26 February 1996 (26.02.96) US 9605642.9 18 March 1996 (18.03.96) GB</b>			
(71) Applicants (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). INDIANA UNIVERSITY FOUNDATION [US/US]; Showalter House, P.O. Box 500, Bloomington, IN 47402 (US).		Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(72) Inventors; and			
(75) Inventors/Applicants (for US only): AMON, Felix, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HARRIS, Alon [US/US]; Showalter House, P.O. Box 500, Bloomington, IN 47402 (US).			
(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).			

(54) Title: USE OF CARBONIC ANHYDRASE INHIBITORS FOR TREATING MACULAR EDEMA

(57) Abstract

There is disclosed a method for treating and/or preventing macular edema and age-related macular degeneration which comprises topical administration of carbonic anhydrase inhibitors to the eye.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

- 1 -

## USE OF CARBONIC ANHYDRASE INHIBITORS FOR TREATING MACULAR EDEMA

### BACKGROUND OF THE INVENTION

Macular edema is swelling within the retina within the critically important central visual zone at the posterior pole of the eye. An accumulation of fluid within the retina tends to distract the neural elements from one another and from their local blood supply, creating a dormancy of visual function in the area. Usually the process is self-limiting, but permanent visual disability occasionally results. Often times, the swelling may take many months to clear. The precise mechanism by which swelling is triggered is uncertain, but it is probable that certain natural metabolic toxins may play an important role in the disease process. Swelling may also follow the implantation of plastic lenses after cataract surgery, particularly if there is a breech in the lens capsule which segregates the vitreous gel from the fluid filled anterior chamber. Long standing macular edema after cataract surgery is one of the most frustrating situations in all of ophthalmology, and is remarkably common.

It was first reported by Cox et al., Arch. Ophthalmol., Vol. 106, Sept. 1988, pp. 1190-95, that oral acetazolamide (DIAMOX®) can cause resolution of chronic macular edema of various causes. In this study, 16 of 41 patients showed a reproducible response to the drug with partial or complete resolution of edema and improvement of visual acuity. The therapeutic effect occurred in more than half of the patients with inherited outer retinal disease or uveitis, but in none with primary retinal vascular disorders. Additional studies have corroborated Cox's findings with acetazolamide (Fishman et al., Arch. Ophthalmol. 1989; 107:1445-1452 and Chen et al., Invest. Ophthalmol. Vis. Sci. 1991; 31:1914-1918) and others have utilized the carbonic anhydrase inhibitor methazolamide (Fishman et al., Arch. Ophthalmol. 1993; 111:1640-1646).

Studies of patients who have proven to be responsive to acetazolamide treatment typically show pigment epithelial cell

- 2 -

dysfunction. These cells, which line the innermost layer of the choroid, have villi-like projections which interdigitate with the retinal photoreceptors. This flexible but intimate association between pigment epithelial cells and photoreceptors is of critical importance to retinal health. The photoreceptors are highly active metabolically and produce waste products at a great rate. The pigment epithelial villi typically absorb catabolites, regenerate photo pigment and provide nutrients via their closely associated choriocapillaris vascular network. Fluorescein angiography of the pigment epithelium in individuals with macular edema who have shown to be responsive to acetazolamide demonstrate leakage of dye into the photoreceptor area. This leakage is inhibited by treatment with acetazolamide.

There are a number of theories as to how carbonic anhydrase inhibitors (CAIs) might work on macular edema however none have been conclusively determined. At least 14 different etiologic subtypes of macular edema exist, and it is probable that some will prove to be more responsive to topical CAI treatment than other types. Some of the abovementioned studies lay a basis for this.

Another even more common chronic condition which has typically been presumed to be irreversible is macular degeneration. Macular degeneration is the most common cause of acquired legal blindness. Instead of fluid accumulating in the outer retina, hard accumulations of lipofuscin, a metabolic waste product, tend to accumulate between the photoreceptors and the villi of the retina pigment epithelium. These accumulations gradually enlarge, and in their early pathologic phase create discrete accumulations known as drusen. The lipofuscin is believed to accumulate as a result of a process known as apoptosis, a breaking off of the photoreceptor elements. Shedding of the cellular components of the photoreceptors is constantly occurring in a healthy retina. Good retinal pigment epithelial metabolism generally insures a rapid clearance of such catabolic byproducts of vision. It is interesting to consider that an improved local circulation or a stabilization of membrane pH gradience might retard or prevent the accumulation of lipofuscin. As drusen accumulate in

- 3 -

number and begin to coalesce, vast areas of retinal photoreceptors become permanently disengaged from their neighboring retinal pigment epithelial villi. The sections of retina so effected become blind. The greatest propensity among the aging population is for drusen to accumulate in the very central area of vision, the macula. Current therapy lacks any substantive clinical scientific basis with zinc in tablet form as one attempted method of treatment. Thus, a method of treating and/or preventing age-related macular degeneration would be welcomed by the medical community.

### SUMMARY OF THE INVENTION

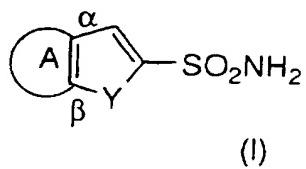
It has now been found that drugs in the class of carbonic anhydrase inhibitors (CAIs) when administered topically are useful in the treatment and/or preventing of macular edema and Age-Related Macular Degeneration (ARMD). CAIs include such drugs as dorzolamide, acetazolamide, methazolamide and other compounds which are described in U.S. Patent Nos. 5,153,192, 5,300,499, 4,797,413, 4,386,098, 4,416,890 and 4,426,388; and in pending patent application 93/16701. The disclosures of the above US patents and patent applications are hereby incorporated by reference. The compounds disclosed in these applications, if able to be formulated as a topical agent, would be considered to be effective in the treatment discussed herein. Dorzolamide, S,S-5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride and its trans enantiomer are useful in the treatment of ocular hypertension associated with glaucoma. CAIs manifest their activity by inhibiting the enzyme, carbonic anhydrase, and impeding their contribution to aqueous humour formation made by the carbonic anhydrase pathway. CAIs block or impede this inflow pathway by inhibiting carbonic anhydrase. Dorzolamide, which is also known under its trademark, TRUSOPT®, is the first topically effective CAI for clinical use.

- 4 -

### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method of treating and/or preventing macular edema by topical application of CAIs to the eye. The present invention is also directed to a method of treating and/or preventing macular degeneration by topical application of CAIs to the eye. In particular, it has been found that Dorzolamide can effectively improve the vision of patients suffering from macular edema.

In particular, the method of treating and/or preventing macular edema and macular degeneration comprises topically administering a compound having the formula:



wherein A together with the two carbon atoms denoted as  $\alpha$  and  $\beta$  is the group



wherein:

X is -S-, -SO-, -SO<sub>2</sub>- or -CH<sub>2</sub>-;

Y is -S-, -O-, or -NR<sup>3</sup>- wherein R<sup>3</sup> is hydrogen, C<sub>1-3</sub>alkyl, or benzyl;

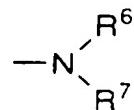
n is 1 or 2;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently selected from:

- 1) hydrogen,
- 2) OR<sup>5</sup> wherein R<sup>5</sup> is:

- a) hydrogen,
- b) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with -OH, or

- 5 -



wherein R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>1-5</sub> alkyl, or joined together form a heterocycle with the nitrogen to which they are attached such as piperidino, morpholino, or piperazino,

- c) C<sub>1-5</sub> alkanoyl, either unsubstituted or substituted with -OH, -NR<sup>6</sup>R<sup>7</sup>, -NH-COR<sup>8</sup> or -COR<sup>8</sup> wherein R<sup>8</sup> is -OH, -NR<sup>6</sup>R<sup>7</sup> or C<sub>1-5</sub> alkoxy,
- d) -CO-R<sup>9</sup>, wherein R<sup>9</sup> is -NR<sup>6</sup>R<sup>7</sup> or a 5- or 6-membered aromatic heterocycle such as pyridyl, imidazolyl, pyrazinyl, thiazolyl, thienyl, or oxazolyl,
- 3) -NR<sup>6</sup>R<sup>7</sup>,
- 4) -NHR<sup>10</sup> wherein R<sup>10</sup> is:
  - a) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,
  - b) -SO<sub>2</sub>R<sup>11</sup>, wherein R<sup>11</sup> is C<sub>1-5</sub> alkyl, or
  - c) -CONR<sup>6</sup>R<sup>7</sup>,
- 5) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with
  - a) -OR<sup>5</sup>,
  - b) -CN,
  - c) -NR<sup>6</sup>R<sup>7</sup>, or
  - d) -COR<sup>8</sup>,
- 6) -SO<sub>2</sub>R<sup>11</sup>,
- 7) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, or

- 6 -

8) -halo, such as chloro, bromo or fluoro;

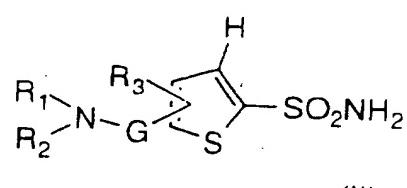
$R^1$  and  $R^3$ , or  $R^2$  and  $R^4$  taken together  
represent a double bond;

$R^1$  and  $R^2$ , or  $R^3$  and  $R^4$  taken together  
represent

- 1) =O, or
- 2) =NOR<sup>12</sup> wherein R<sup>12</sup> is hydrogen or C<sub>1-3</sub>alkyl; and one of the -CH<sub>2</sub>- groups of -(CH<sub>2</sub>)<sub>n</sub>- can be substituted with -COR<sup>8</sup>, -CH<sub>2</sub>R<sup>8</sup>, or -CH<sub>2</sub>COR<sup>8</sup>.

The compounds of formula I are described in and prepared by methods set forth in U.S. Patent No. 4,797,413, the disclosure of which is hereby incorporated by reference.

Additionally, the method comprises topically administering a thiophene sulfonamide compound having the formula:



or a pharmaceutically acceptable salt thereof wherein;

$R_1$  is H; C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>.

$R_2$  is H; C<sub>1-8</sub> alkyl; C<sub>2-8</sub> alkyl substituted with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>3-7</sub> alkenyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>3-7</sub> alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>,

- 7 -

or Cl-4 alkoxy; Cl-3 alkyl substituted with phenyl or heteroaryl which can be unsubstituted or substituted optionally with OH, C(H<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, Cl-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; C<sub>2</sub>-4 alkoxy substituted optionally with NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, or C(=O)R<sub>7</sub>; phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, Cl-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; provided that R<sub>1</sub> and R<sub>2</sub> cannot both be H; or R<sub>1</sub> and R<sub>2</sub>; can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, C(=O)R<sub>7</sub>, Cl-6 alkyl, Cl-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, C(=O)R<sub>7</sub> or on nitrogen with NR<sub>5</sub>R<sub>6</sub>, Cl-4 alkoxy, C(=O)R<sub>7</sub>, Cl-6 alkyl or C<sub>2</sub>-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy or C(=O)R<sub>7</sub>.

R<sub>3</sub> is       H; halogen; Cl-4 alkyl; Cl-8 alkoxy; Cl-8 alkylthiol; C<sub>2</sub>-8 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy or C(=O)R<sub>7</sub>; Cl-4 alkyl substituted optionally with R<sub>4</sub>; or R<sub>1</sub> and R<sub>3</sub> can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R<sub>4</sub>.

R<sub>4</sub> is       OH; Cl-4 alkyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub> halogen, Cl-4 alkoxy or C(=O)R<sub>7</sub>; Cl-4 alkoxy; C<sub>2</sub>-4 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy or C(=O)R<sub>7</sub>, NR<sub>5</sub>R<sub>6</sub> phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, Cl-4 alkoxy, Cl-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2;  
provided that when R<sub>3</sub> is in the 4 position and is H or halogen then R<sub>1</sub> and R<sub>2</sub> are not H, Cl-6 alkyl substituted optionally with OH, Cl-6 alkoxy, C<sub>2</sub>-6 alkoxycarbonyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms

- 8 -

selected optionally from C, O, S, N in which said nitrogen, when saturated is substituted optionally with H or C<sub>1-6</sub> alkyl or in which said carbon is substituted optionally with C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or OH and when R<sub>3</sub> is in the 5 position and is H, Cl, Br, or C<sub>1-3</sub> alkyl then neither R<sub>1</sub> nor R<sub>2</sub> can be H or C<sub>1-4</sub> alkyl.

R<sub>5</sub> and R<sub>6</sub> are the same or different and are H; C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>1-4</sub> alkoxy C<sub>2-4</sub> alkoxy substituted optionally with OH, halogen; C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>3-7</sub> alkenyl unsubstituted or substituted optionally with OH; NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub>alkoxy; C<sub>3-7</sub>alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub>alkoxy; C<sub>1-2</sub>alkylC<sub>1-3</sub>cycloalkyl or R<sub>5</sub> and R<sub>6</sub> can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C<sub>1-4</sub>; alkoxy, C(=O)R<sub>7</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy C(=O)R<sub>7</sub> or on nitrogen with C<sub>1-4</sub> alkoxy, C(=O)R<sub>7</sub> S(=O)<sub>m</sub>R<sub>8</sub>, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy, C(=O)R<sub>7</sub> or on sulfur by (=O)<sub>m</sub> wherein m is 0-2.

R<sub>7</sub> is           C<sub>1-8</sub> alkyl; C<sub>1-8</sub> alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>9</sub>, C<sub>1-4</sub>alkoxy; C<sub>2-4</sub> alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen or C<sub>1-4</sub> alkoxy; or NR<sub>5</sub>R<sub>6</sub>.

R<sub>8</sub> is           C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>.

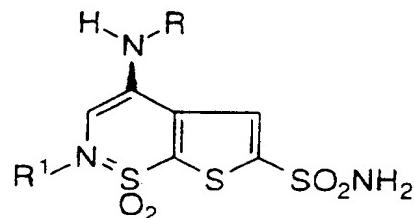
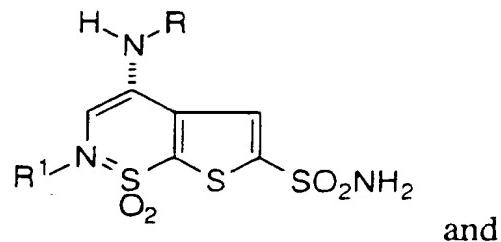
R<sub>9</sub> is           C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkoxy amino, C<sub>1-3</sub> alkylamino, or di-C<sub>1-3</sub> alkylamino; and

G is           C(=O) or SO<sub>2</sub>.

The compounds of formula II are described in and prepared by methods set forth in U.S. Patent No. 5,153,192, the disclosure of which is hereby incorporated by reference.

- 9 -

Preferred compounds of formula II include compounds of the formula



wherein R is selected from -CH<sub>2</sub>CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>1</sup> is selected from CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2</sub>-4 or a pharmaceutically acceptable salt thereof.

The present invention is based upon the discovery that CAIs when administered topically can resolve macular edemas of various causes. It was found that a patient was quickly able to improve visual acuity as measured by an increase in the number of lines the patient was able to read on the standard eye chart after 40 days of topical treatment with a CAI.

Research was done using TRUSOPT®, a particular carbonic anhydrase inhibitor. It is a known compound useful for the reduction of intraocular pressure as described in U.S. Pat. No. 4,797,413.

The CAI used is preferably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as solutions, ointments or as a solid insert. Formulations of this compound may contain from 0.01 to 5% and especially 0.5 to 2% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the

- 10 -

dose is effective in increasing blood flow velocity. For a single dose, from between 0.001 to 5.0 mg, preferably 0.005 to 2.0 mg, and especially 0.005 to 1.0 mg of the compound is applied to the human eye.

The pharmaceutical preparation which contains the compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a non-toxic pharmaceutical inorganic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, bacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetracetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, (hydroxylaralkyl cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl

- 11 -

cellulose; acrylates such as polyacrylic acid salts, ethylacrylates, polyactylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxymethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, and mixtures of said polymer.

Preferably the solid insert is prepared from cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose or hydroxypropylmethyl cellulose or from other synthetic materials such as polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene oxide or polyvinyl methylether.

Hydroxypropyl cellulose, one of the preferred polymers for the preparation of the insert is available in several polymeric forms, all of which are suitable in the preparation of these inserts. Thus, the product sold by Hercules, Inc. of Wilmington, Delaware under the name KLUCEL™ such as KLUCEL HF, HWF, MF, GF, JF, LF and EF which are intended for food or pharmaceutical use are particularly useful. The molecular weight of these polymers useful for the purposes described herein may be at least 30,000 to about 1,000,000 or more. Similarly, an ethylene oxide polymer having a molecular weight of up to 5,000,000 or greater, and preferably 100,000 to 5,000,000 can be employed. Further, for example, POLYOXTM a polymer supplied by Union Carbide Co. may be used having a molecular weight of about 50,000 to 5,000,000 or more and preferably 3,000,000 to 4,000,000. Other specific polymers which are useful are polyvinyl pyrrolidone having a molecular weight of from about 10,000 to about 1,000,000 or more, preferably up to about 350,000 and especially about 20,000 to 60,000; polyvinyl alcohol having a molecular weight of from about 30,000 to 1,000,000 or more, particularly about 400,000 and especially from about 100,000 to about 200,000; hydroxypropylmethyl cellulose having a molecular weight of from about 10,000 to 1,000,000 or more, particularly up to about 200,000 and especially about 80,000 to about 125,000; methyl cellulose having a molecular weight of from about

- 12 -

10,000 to about 1,000,000 or more, preferably up to about 200,000 and especially about 50 to 100,000; and CARBOPOL™ (carboxyvinyl polymer) of B. F. Goodrich and Co. designated as grades 934,940 and 941.

It is clear that for the purpose of this invention the type and molecular weight of the polymer is not critical. Any water soluble polymers can be used having an average molecular weight which will afford dissolution of the polymer and accordingly the medicament in any desired length of time. The inserts, therefore, can be prepared to allow for retention and accordingly effectiveness in the eye for any desired period. The insert can be in the form of a square, rectangle, oval, circle, doughnut, semi-circle, 1/4 moon shape, and the like. Preferably the insert is in the form of a rod, doughnut, oval or 1/4 moon. The insert can be readily prepared, for example, by dissolving the medicament and the polymer in a suitable solvent and the solution evaporated to afford a thin film of the polymer which can then be subdivided to prepare inserts of appropriate size. Alternatively the insert can be prepared by warming the polymer and the medicament and the resulting mixture molded to form a thin film. Preferably, the inserts are prepared by molding or extrusion procedures well known in the art. The molded or extruded product can then be subdivided to afford inserts of suitable size for administration in the eye. The insert can be of any suitable size to readily fit into the eye. For example, castings or compression molded films having a thickness of about 0.25 mm to 15.0 mm can be subdivided to obtain suitable inserts. Rectangular segments of the cast or compressed film having a thickness between about 0.5 and 1.5 mm can be cut to afford shapes such as rectangular plates of 4x5-20 mm or ovals of comparable size. Similarly, extruded rods having a diameter between about 0.5 and 1.5 mm can be cut into suitable sections to provide the desired amount of polymer. For example, rods of 1.0 to 1.5 mm in diameter and about 20 mm long are found to be satisfactory. The inserts may also be directly formed by injection molding. It is preferred that the ophthalmic inserts containing the medicament of the present invention be formed so that

- 13 -

they are smooth and do not have any sharp edges or corners which could cause damage to the eye. Since the term smooth and sharp edges or corners are subjective terms, in this application these terms are used to indicate that excessive irritation of the eye will not result from the use of the insert.

The ocular medicinal inserts can also contain plasticizers, buffering agents and preservatives. Plasticizers suitable for this purpose must, of course, also be completely soluble in the lacrimal fluids of the eye. Examples of suitable plasticizers that might be mentioned are water, polyethylene glycol, propylene glycol, glycerine, trimethylol propane, di and tripropylene glycol, hydroxypropyl sucrose and the like. Typically, such plasticizers can be present in the ophthalmic insert in an amount ranging from up to 1 about 30% by weight. A particularly preferred plasticizer is water which is present in amounts of at least about 5% up to about 40%. In actual practice, a water content of from about 10% to about 20% is preferred since it may be easily accomplished and adds the desired softness and pliability to the insert.

When plasticizing the solid medicinal product with water, the product is contacted with air having a relative humidity of at least 40% until said product picks up at least about 5% water and becomes softer and more pliable. In a preferred embodiment, the relative humidity of the air is from about 60% to about 99% and the contacting is continued until the water is present in the product in amounts of from about 10% to about 20%.

Suitable water soluble preservatives which may be employed in the insert are sodium bisulfate, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric borate, parabens, benzyl alcohol and phenylethanol. These agents may be present in amounts of from about 0.001 to about 5% by weight of solid insert, and preferably about 0.1 to about 2%.

Suitable water soluble buffering agents are alkali, alkali earth carbonates, phosphates, bicarbonates, citrates, borates, and the

- 14 -

like, such as sodium phosphate, citrate, borate, acetate, bicarbonate and carbonate. These agents may be present in amounts sufficient to obtain a pH of the system of between about 5.5 to about 8.0 and especially about 7 to about 8; usually up to about 2% by weight of polymer. The insert may contain from about 1 mg to about 100 mg of water soluble polymer, more particularly from about 5 to about 50 mg and especially from about 5 to about 20 mg. The medicament is present from about 0.1 to about 25% by weight of insert.

The claimed use of topical carbonic anhydrase inhibitors to treat and prevent macular edema has been the subject of a study to determine whether TRUSOPT® drops were effective as a treatment for cystoid macular edema. In the study, a subject with cystoid macular edema in both eyes was administered TRUSOPT® eye drops twice daily as monotherapy. At the pre-treatment fluorescein angiography examination, the patient presented in the early transit a diffuse leakage of dye out of ectatic retinal capillaries widespread over the posterior pole inducing an intensive fuzzy fluorescence. During midtransit, filling of midsized retinal foveal cysts occurred. After 40 days, the patient underwent fluorescein angiography to determine if the therapy had any effect on the edema. The post-treatment fluorescein angiography presented reduced leakage and primarily small and packed aggregate retinal cysts as well as a reading acuity improvement of four lines in the Snellen chart.

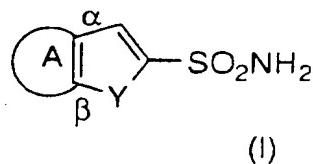
o

- 15 -

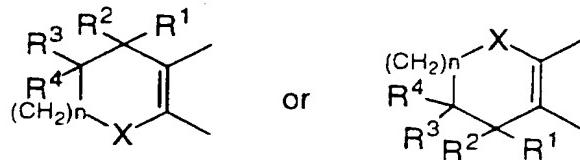
WHAT IS CLAIMED IS:

1. A method for treating macular edema which comprises applying to the eye an effective amount of a topical carbonic anhydrase inhibitor.

2. The method according to Claim 1 wherein the carbonic anhydrase inhibitor is a compound of the formula



wherein A together with the two carbon atoms denoted as  $\alpha$  and  $\beta$  is the group



wherein:

X is -S-, -SO-, -SO<sub>2</sub>- or -CH<sub>2</sub>-;

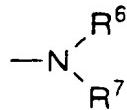
Y is -S-, -O-, or -NR<sup>3</sup>- wherein R<sup>3</sup> is hydrogen, C<sub>1-3</sub>alkyl, or benzyl;

n is 1 or 2;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently selected from:

- 1) hydrogen,
- 2) OR<sup>5</sup> wherein R<sup>5</sup> is:

- a) hydrogen,
- b) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with -OH, or



- 16 -

wherein R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>1-5</sub> alkyl, or joined together form a heterocycle with the nitrogen to which they are attached such as piperidino, morpholino, or piperazino,

- c) C<sub>1-5</sub> alkanoyl, either unsubstituted or substituted with -OH, -NR<sup>6</sup>R<sup>7</sup>, -NH-COR<sup>8</sup> or -COR<sup>8</sup> wherein R<sup>8</sup> is -OH, -NR<sup>6</sup>R<sup>7</sup> or C<sub>1-5</sub> alkoxy,
- d) -CO-R<sup>9</sup>, wherein R<sup>9</sup> is -NR<sup>6</sup>R<sup>7</sup> or a 5- or 6-membered aromatic heterocycle such as pyridyl, imidazolyl, pyrazinyl, thiazolyl, thienyl, or oxazolyl,
- 3) -NR<sup>6</sup>R<sup>7</sup>,
- 4) -NHR<sup>10</sup> wherein R<sup>10</sup> is:
  - a) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,
  - b) -SO<sub>2</sub>R<sup>11</sup>, wherein R<sup>11</sup> is C<sub>1-5</sub> alkyl, or
  - c) -CONR<sup>6</sup>R<sup>7</sup>,
- 5) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with
  - a) -OR<sup>5</sup>,
  - b) -CN,
  - c) -NR<sup>6</sup>R<sup>7</sup>, or
  - d) -COR<sup>8</sup>,
- 6) -SO<sub>2</sub>R<sup>11</sup>,
- 7) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, or
- 8) -halo, such as chloro, bromo or fluoro;

R<sup>1</sup> and R<sup>3</sup>, or R<sup>2</sup> and R<sup>4</sup> taken together

- 17 -

represent a double bond;

$R^1$  and  $R^2$ , or  $R^3$  and  $R^4$  taken together

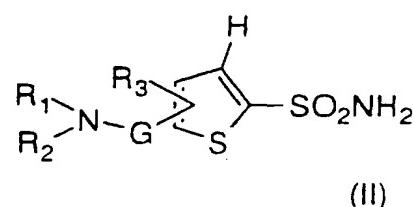
represent

1) =O, or

2) =NOR<sup>12</sup> wherein R<sup>12</sup> is hydrogen or C<sub>1-3</sub>alkyl; and one of the -CH<sub>2</sub>- groups of -(CH<sub>2</sub>)<sub>n</sub>- can be substituted with -COR<sup>8</sup>, -CH<sub>2</sub>R<sup>8</sup>, or -CH<sub>2</sub>COR<sup>8</sup>;

or a pharmaceutically acceptable salt thereof.

3. The method according to Claim 1 wherein the carbonic anhydrase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof wherein;

$R_1$  is H; C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>.

$R_2$  is H; C<sub>1-8</sub> alkyl; C<sub>2-8</sub> alkyl substituted with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>3-7</sub> alkenyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>3-7</sub> alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>1-3</sub> alkyl substituted with phenyl or heteroaryl which can be unsubstituted or substituted optionally with OH, C(H<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; C<sub>2-4</sub> alkoxy substituted optionally with NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy, or C(=O)R<sub>7</sub>; phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub>

- 18 -

haloalkoxy,  $C(=O)R_7$ ,  $S(=O)mR_8$  or  $SO_2NR_5R_6$ , wherein  $m$  is 0-2 and  $n$  is 0-2; provided that  $R_1$  and  $R_2$  cannot both be H; or  $R_1$  and  $R_2$ ; can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH,  $NR_5R_6$ , halogen,  $C_1$ -4alkoxy,  $C(=O)R_7$ ,  $C_1$ -6 alkyl,  $C_1$ -6 alkyl substituted optionally with OH,  $NR_5R_6$ , halogen,  $C_1$ -4 alkoxy,  $C(=O)R_7$  or on nitrogen with  $NR_5R_6$ ,  $C_1$ -4alkoxy,  $C(=O)R_7$ ,  $C_1$ -6 alkyl or  $C_2$ -6 alkyl substituted optionally with OH,  $NR_5R_6$ , halogen,  $C_1$ -4 alkoxy or  $C(=O)R_7$ .

$R_3$  is      H; halogen;  $C_1$ -4 alkyl;  $C_1$ -8 alkoxy;  $C_1$ -8 alkylthiol;  $C_2$ -8 alkoxy substituted optionally with OH,  $NR_5R_6$ , halogen,  $C_1$ -4 alkoxy or  $C(=O)R_7$ ;  $C_1$ -4 alkyl substituted optionally with  $R_4$ ; or  $R_1$  and  $R_3$  can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with  $R_4$ .

$R_4$  is      OH;  $C_1$ -4 alkyl unsubstituted or substituted optionally with OH,  $NR_5R_6$  halogen,  $C_1$ -4 alkoxy or  $C(=O)R_7$ ;  $C_1$ -4 alkoxy;  $C_2$ -4 alkoxy substituted optionally with OH,  $NR_5R_6$ , halogen,  $C_1$ -4 alkoxy or  $C(=O)R_7$ ,  $NR_5R_6$  phenyl, or heteroaryl, unsubstituted or substituted optionally with OH,  $(CH_2)_nNR_5R_6$ , halogen,  $C_1$ -4 alkoxy,  $C_1$ -4 haloalkoxy,  $C(=O)R_7$ ,  $S(=O)mR_8$  or  $SO_2NR_5R_6$ , wherein  $m$  is 0-2 and  $n$  is 0-2;

provided that when  $R_3$  is in the 4 position and is H or halogen then  $R_1$  and  $R_2$  are not H,  $C_1$ -6 alkyl substituted optionally with OH,  $C_1$ -6 alkoxy,  $C_2$ -6 alkoxy carbonyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated is substituted optionally with H or  $C_1$ -6 alkyl or in which said carbon is substituted optionally with  $C_1$ -6 alkyl,  $C_1$ -6 alkoxy or OH and when  $R_3$  is in the 5 position and is H, Cl, Br, or  $C_1$ -3 alkyl then neither  $R_1$  nor  $R_2$  can be H or  $C_1$ -4 alkyl.

$R_5$  and  $R_6$  are the same or different and are H;  $C_1$ -4 alkyl;  $C_2$ -4 alkyl substituted optionally with OH, halogen,  $C_1$ -4 alkoxy or  $C(=O)R_7$ ;

- 19 -

C<sub>1</sub>-4 alkoxy C<sub>2</sub>-4 alkoxy substituted optionally with OH, halogen; C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>3</sub>-7 alkenyl unsubstituted or substituted optionally with OH; NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4alkoxy; C<sub>3</sub>-7alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4alkoxy; C<sub>1</sub>-2alkylC<sub>1</sub>-3cycloalkyl or R<sub>5</sub> and R<sub>6</sub> can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C<sub>1</sub>-4; alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy C(=O)R<sub>7</sub> or on nitrogen with C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> S(=O)<sub>m</sub>R<sub>8</sub>, C<sub>1</sub>-6 alkyl or C<sub>2</sub>-6 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> or on sulfur by (=O)<sub>m</sub> wherein m is 0-2.

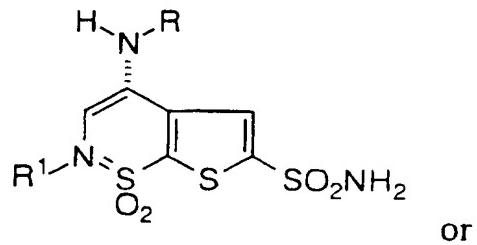
R<sub>7</sub> is      C<sub>1</sub>-8 alkyl; C<sub>1</sub>-8 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>9</sub>, C<sub>1</sub>-4alkoxy; C<sub>2</sub>-4 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen or C<sub>1</sub>-4 alkoxy; or NR<sub>5</sub>R<sub>6</sub>.

R<sub>8</sub> is      C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

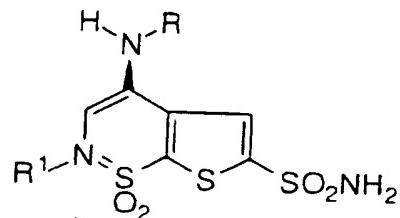
R<sub>9</sub> is      C<sub>1</sub>-4 alkyl; C<sub>1</sub>-4 alkoxy amino, C<sub>1</sub>-3 alkylamino, or di-C<sub>1</sub>-3 alkylamino; and

G is      C(=O) or SO<sub>2</sub>.

4. The method according to Claim 3 wherein the carbonic anhydrase inhibitor is selected from a compound of the formula



- 20 -



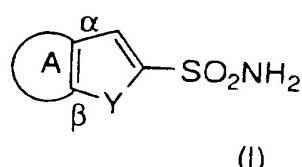
wherein R is selected from -CH<sub>2</sub>CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>1</sup> is selected from CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2-4</sub> or a pharmaceutically acceptable salt thereof.

5. The method according to Claim 1 wherein the carbonic anhydrase inhibitor comprises dorzolamide, acetazolamide and methazolamide.

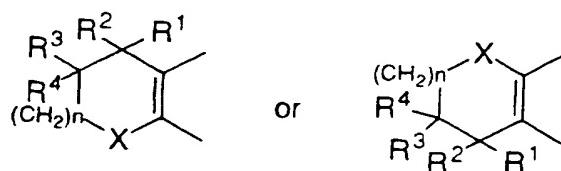
6. The method according to Claim 5 wherein the carbonic anhydrase inhibitor is dorzolamide.

7. A method for preventing macular edema which comprises applying to the eye an effective amount of a topical carbonic anhydrase inhibitor.

8. The method according to Claim 7 wherein the carbonic anhydrase inhibitor is a compound of the formula



wherein A together with the two carbon atoms denoted as α and β is the group



- 21 -

wherein:

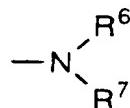
X is -S-, -SO-, -SO<sub>2</sub>- or -CH<sub>2</sub>-;

Y is -S-, -O-, or -NR<sup>3</sup>- wherein R<sup>3</sup> is hydrogen, C<sub>1-3</sub>alkyl, or benzyl;

n is 1 or 2;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently selected from:

- 1) hydrogen,
- 2) OR<sup>5</sup> wherein R<sup>5</sup> is:
  - a) hydrogen,
  - b) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with -OH, or



wherein R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>1-5</sub> alkyl, or joined together form a heterocycle with the nitrogen to which they are attached such as piperidino, morpholino, or

- c) piperazino,
- c) C<sub>1-5</sub> alkanoyl, either unsubstituted or substituted with -OH, -NR<sup>6</sup>R<sup>7</sup>, -NH-COR<sup>8</sup> or -COR<sup>8</sup> wherein R<sup>8</sup> is -OH, -NR<sup>6</sup>R<sup>7</sup> or C<sub>1-5</sub> alkoxy,
- d) -CO-R<sup>9</sup>, wherein R<sup>9</sup> is -NR<sup>6</sup>R<sup>7</sup> or a 5- or 6-membered aromatic heterocycle such as pyridyl, imidazolyl, pyrazinyl, thiazolyl, thienyl, or oxazolyl,
- 3) -NR<sup>6</sup>R<sup>7</sup>,
- 4) -NHR<sup>10</sup> wherein R<sup>10</sup> is:

- 22 -

- a)  $-\text{SO}_2\text{NR}^6\text{R}^7$ ,
- b)  $-\text{SO}_2\text{R}^{11}$ , wherein  $\text{R}^{11}$  is  $\text{C}_{1-5}$  alkyl, or
- c)  $-\text{CONR}^6\text{R}^7$ ,
- 5)  $\text{C}_{1-5}$  alkyl, either unsubstituted or substituted with
  - a)  $-\text{OR}^5$ ,
  - b)  $-\text{CN}$ ,
  - c)  $-\text{NR}^6\text{R}^7$ , or
  - d)  $-\text{COR}^8$ ,
- 6)  $-\text{SO}_2\text{R}^{11}$ ,
- 7)  $-\text{SO}_2\text{NR}^6\text{R}^7$ , or
- 8) -halo, such as chloro, bromo or fluoro;

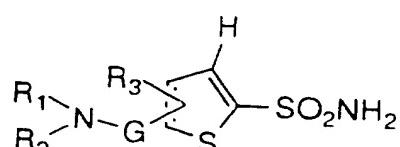
$\text{R}^1$  and  $\text{R}^3$ , or  $\text{R}^2$  and  $\text{R}^4$  taken together represent a double bond;

$\text{R}^1$  and  $\text{R}^2$ , or  $\text{R}^3$  and  $\text{R}^4$  taken together represent

- 1)  $=\text{O}$ , or
- 2)  $=\text{NOR}^{12}$  wherein  $\text{R}^{12}$  is hydrogen or  $\text{C}_{1-3}$ alkyl; and one of the  $-\text{CH}_2-$  groups of  $-(\text{CH}_2)_n-$  can be substituted with  $-\text{COR}^8$ ,  $-\text{CH}_2\text{R}^8$ , or  $-\text{CH}_2\text{COR}^8$ ;

or a pharmaceutically acceptable salt thereof.

9. The method according to Claim 7 wherein the carbonic anhydrase inhibitor is a compound of the formula



(II)

- 23 -

or a pharmaceutically acceptable salt thereof wherein;

R<sub>1</sub> is H; C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

R<sub>2</sub> is H; C<sub>1</sub>-8 alkyl; C<sub>2</sub>-8 alkyl substituted with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>3</sub>-7 alkenyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>3</sub>-7 alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>1</sub>-3 alkyl substituted with phenyl or heteroaryl which can be unsubstituted or substituted optionally with OH, C(H<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; C<sub>2</sub>-4 alkoxy substituted optionally with NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, or C(=O)R<sub>7</sub>; phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; provided that R<sub>1</sub> and R<sub>2</sub> cannot both be H; or R<sub>1</sub> and R<sub>2</sub>; can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> or on nitrogen with NR<sub>5</sub>R<sub>6</sub>, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl or C<sub>2</sub>-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

R<sub>3</sub> is H; halogen; C<sub>1</sub>-4 alkyl; C<sub>1</sub>-8 alkoxy; C<sub>1</sub>-8 alkylthiol; C<sub>2</sub>-8 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkyl substituted optionally with R<sub>4</sub>; or R<sub>1</sub> and R<sub>3</sub> can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R<sub>4</sub>.

R<sub>4</sub> is OH; C<sub>1</sub>-4 alkyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub> halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkoxy; C<sub>2</sub>-4

- 24 -

alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>, NR<sub>5</sub>R<sub>6</sub> phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2;

provided that when R<sub>3</sub> is in the 4 position and is H or halogen then R<sub>1</sub> and R<sub>2</sub> are not H, C<sub>1-6</sub> alkyl substituted optionally with OH, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkoxy carbonyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated is substituted optionally with H or C<sub>1-6</sub> alkyl or in which said carbon is substituted optionally with C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or OH and when R<sub>3</sub> is in the 5 position and is H, Cl, Br, or C<sub>1-3</sub> alkyl then neither R<sub>1</sub> nor R<sub>2</sub> can be H or C<sub>1-4</sub> alkyl.

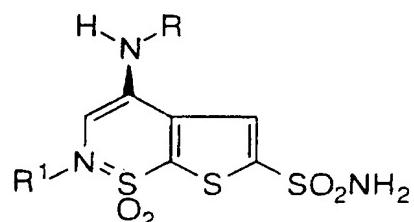
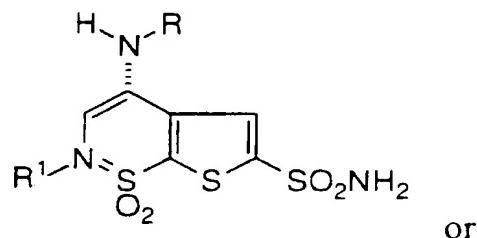
R<sub>5</sub> and R<sub>6</sub> are the same or different and are H; C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>1-4</sub> alkoxy C<sub>2-4</sub> alkoxy substituted optionally with OH, halogen; C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>3-7</sub> alkenyl unsubstituted or substituted optionally with OH; NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>3-7</sub> alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>1-2</sub> alkyl C<sub>1-3</sub> cycloalkyl or R<sub>5</sub> and R<sub>6</sub> can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C<sub>1-4</sub>; alkoxy, C(=O)R<sub>7</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy C(=O)R<sub>7</sub> or on nitrogen with C<sub>1-4</sub> alkoxy, C(=O)R<sub>7</sub> S(=O)<sub>m</sub>R<sub>8</sub>, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy, C(=O)R<sub>7</sub> or on sulfur by (=O)<sub>m</sub> wherein m is 0-2.

R<sub>7</sub> is C<sub>1-8</sub> alkyl; C<sub>1-8</sub> alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>9</sub>, C<sub>1-4</sub> alkoxy; C<sub>2-4</sub> alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen or C<sub>1-4</sub> alkoxy; or R<sub>5</sub>R<sub>6</sub>.

- 25 -

- R8 is C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.  
 R9 is C<sub>1</sub>-4 alkyl; C<sub>1</sub>-4 alkoxy amino, C<sub>1</sub>-3 alkylamino, or di-C<sub>1</sub>-3 alkylamino; and  
 G is C(=O) or SO<sub>2</sub>.

10. The method according to Claim 9 wherein the carbonic anhydrase inhibitor is selected from a compound of the formula



wherein R is selected from -CH<sub>2</sub>CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>1</sup> is selected from CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2</sub>-4 or a pharmaceutically acceptable salt thereof.

11. The method according to Claim 7 wherein the carbonic anhydrase inhibitor comprises dorzolamide, acetazolamide and methazolamide.

12. The method according to Claim 11 wherein the carbonic anhydrase inhibitor is dorzolamide.

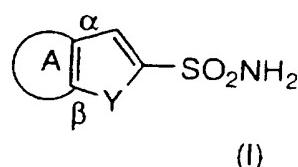
- 26 -

13. A method for treating age-related macular degeneration which comprises applying to the eye an effective amount of a topical carbonic anhydrase inhibitor.

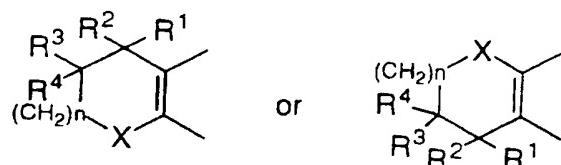
14. The method according to Claim 13 wherein the carbonic anhydrase inhibitor comprises dorzolamide, acetazolamide and methazolamide.

15. The method according to Claim 13 wherein the carbonic anhydrase inhibitor is dorzolamide.

16. The method according to Claim 13 wherein the carbonic anhydrase inhibitor is a compound of the formula



wherein A together with the two carbon atoms denoted as  $\alpha$  and  $\beta$  is the group



wherein:

X is  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-CH_2-$ ;

Y is  $-S-$ ,  $-O-$ , or  $-NR^3-$  wherein  $R^3$  is hydrogen,  $C_{1-3}$ alkyl, or benzyl;

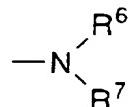
n is 1 or 2;

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  are independently selected from:

- 1) hydrogen,
- 2)  $OR^5$  wherein  $R^5$  is:
  - a) hydrogen,

- 27 -

- b) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with -OH, or



wherein R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>1-5</sub> alkyl, or joined together form a heterocycle with the nitrogen to which they are attached such as piperidino, morpholino, or piperazino,

- c) C<sub>1-5</sub> alkanoyl, either unsubstituted or substituted with -OH, -NR<sup>6</sup>R<sup>7</sup>, -NH-COR<sup>8</sup> or -COR<sup>8</sup> wherein R<sup>8</sup> is -OH, -NR<sup>6</sup>R<sup>7</sup> or C<sub>1-5</sub> alkoxy,

- d) -CO-R<sup>9</sup>, wherein R<sup>9</sup> is -NR<sup>6</sup>R<sup>7</sup> or a 5- or 6-membered aromatic heterocycle such as pyridyl, imidazolyl, pyrazinyl, thiazolyl, thienyl, or oxazolyl,

3) -NR<sup>6</sup>R<sup>7</sup>,

4) -NHR<sup>10</sup> wherein R<sup>10</sup> is:

a) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,

b) -SO<sub>2</sub>R<sup>11</sup>, wherein R<sup>11</sup> is C<sub>1-5</sub> alkyl, or

c) -CONR<sup>6</sup>R<sup>7</sup>.

- 5) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with

a) -OR<sup>5</sup>,

b) -CN,

c) -NR<sup>6</sup>R<sup>7</sup>, or

d) -COR<sup>8</sup>,

6) -SO<sub>2</sub>R<sup>11</sup>,

- 28 -

7)  $-\text{SO}_2\text{NR}^6\text{R}^7$ , or

8) -halo, such as chloro, bromo or fluoro;

$\text{R}^1$  and  $\text{R}^3$ , or  $\text{R}^2$  and  $\text{R}^4$  taken together  
represent a double bond;

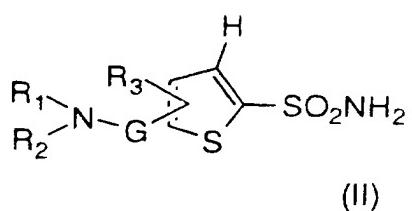
$\text{R}^1$  and  $\text{R}^2$ , or  $\text{R}^3$  and  $\text{R}^4$  taken together  
represent

1)  $=\text{O}$ , or

2)  $=\text{NOR}^{12}$  wherein  $\text{R}^{12}$  is hydrogen or  
 $\text{C}_{1-3}\text{alkyl}$ ; and one of the  $-\text{CH}_2-$   
groups of  $-(\text{CH}_2)_n-$  can be substituted with  
 $-\text{COR}^8$ ,  $-\text{CH}_2\text{R}^8$ , or  $-\text{CH}_2\text{COR}^8$ ;

or a pharmaceutically acceptable salt thereof.

17. The method according to Claim 13 wherein the carbonic anhydrase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof wherein;

$\text{R}^1$  is H; C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>.

$\text{R}^2$  is H; C<sub>1-8</sub> alkyl; C<sub>2-8</sub> alkyl substituted with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>; C<sub>3-7</sub> alkenyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>3-7</sub> alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1-4</sub> alkoxy; C<sub>1-3</sub> alkyl substituted with phenyl or heteroaryl which can be unsubstituted or substituted optionally with OH,

- 29 -

$C(H_2)_nNR_5R_6$ , halogen, Cl-4 alkoxy, Cl-4 haloalkoxy,  $C(=O)R_7$ ,  $S(=O)_mR_8$  or  $SO_2NR_5R_6$ , wherein m is 0-2 and n is 0-2; C2-4 alkoxy substituted optionally with NR5R6, halogen, Cl-4 alkoxy, or  $C(=O)R_7$ ; phenyl, or heteroaryl, unsubstituted or substituted optionally with OH,  $(CH_2)_nNR_5R_6$ , halogen, Cl-4 alkoxy, Cl-4 haloalkoxy,  $C(=O)R_7$ ,  $S(=O)_mR_8$  or  $SO_2NR_5R_6$ , wherein m is 0-2 and n is 0-2; provided that R1 and R2 cannot both be H; or R1 and R2; can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, NR5R6, halogen, Cl-4 alkoxy,  $C(=O)R_7$ , Cl-6 alkyl, Cl-6 alkyl substituted optionally with OH, NR5R6, halogen, Cl-4 alkoxy,  $C(=O)R_7$  or on nitrogen with NR5R6, Cl-4 alkoxy,  $C(=O)R_7$ , Cl-6 alkyl or C2-6 alkyl substituted optionally with OH, NR5R6, halogen, Cl-4 alkoxy or  $C(=O)R_7$ .

R3 is       H; halogen; Cl-4 alkyl; Cl-8 alkoxy; Cl-8 alkylthiol; C2-8 alkoxy substituted optionally with OH, NR5R6, halogen, Cl-4 alkoxy or  $C(=O)R_7$ ; Cl-4 alkyl substituted optionally with R4; or R1 and R3 can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R4.

R4 is       OH; Cl-4 alkyl unsubstituted or substituted optionally with OH, NR5R6 halogen, Cl-4 alkoxy or  $C(=O)R_7$ ; Cl-4 alkoxy; C2-4 alkoxy substituted optionally with OH, NR5R6, halogen, Cl-4 alkoxy or  $C(=O)R_7$ , NR5R6 phenyl, or heteroaryl, unsubstituted or substituted optionally with OH,  $(CH_2)_nNR_5R_6$ , halogen, Cl-4 alkoxy, Cl-4 haloalkoxy,  $C(=O)R_7$ ,  $S(=O)_mR_8$  or  $SO_2NR_5R_6$ , wherein m is 0-2 and n is 0-2;

provided that when R3 is in the 4 position and is H or halogen then R1 and R2 are not H, Cl-6 alkyl substituted optionally with OH, Cl-6 alkoxy, C2-6 alkoxycarbonyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated is substituted optionally with H or Cl-6 alkyl or in

- 30 -

which said carbon is substituted optionally with C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkoxy or OH and when R<sub>3</sub> is in the 5 position and is H, Cl, Br, or C<sub>1</sub>-3 alkyl then neither R<sub>1</sub> nor R<sub>2</sub> can be H or C<sub>1</sub>-4 alkyl.

R<sub>5</sub> and R<sub>6</sub> are the same or different and are H; C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkoxy C<sub>2</sub>-4 alkoxy substituted optionally with OH, halogen; C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>3</sub>-7 alkenyl unsubstituted or substituted optionally with OH; NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4alkoxy; C<sub>3</sub>-7alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4alkoxy; C<sub>1</sub>-2alkylC<sub>1</sub>-3cycloalkyl or R<sub>5</sub> and R<sub>6</sub> can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C<sub>1</sub>-4; alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy C(=O)R<sub>7</sub> or on nitrogen with C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> S(=O)<sub>m</sub>R<sub>8</sub>, C<sub>1</sub>-6 alkyl or C<sub>2</sub>-6 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> or on sulfur by (=O)<sub>m</sub> wherein m is 0-2.

R<sub>7</sub> is      C<sub>1</sub>-8 alkyl; C<sub>1</sub>-8 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>9</sub>, C<sub>1</sub>-4alkoxy; C<sub>2</sub>-4 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen or C<sub>1</sub>-4 alkoxy; or NR<sub>5</sub>R<sub>6</sub>.

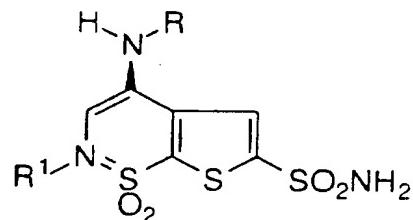
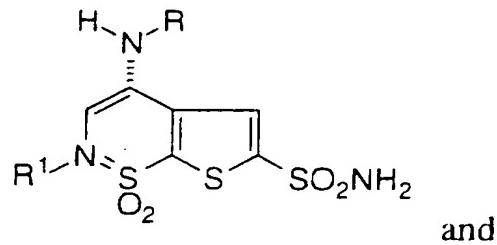
R<sub>8</sub> is      C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

R<sub>9</sub> is      C<sub>1</sub>-4 alkyl; C<sub>1</sub>-4 alkoxy amino, C<sub>1</sub>-3 alkylamino, or di-C<sub>1</sub>-3 alkylamino; and

G is      C(=O) or SO<sub>2</sub>.

18. The method according to Claim 13 wherein the carbonic anhydrase inhibitor is selected from a compound of the formula

- 31 -



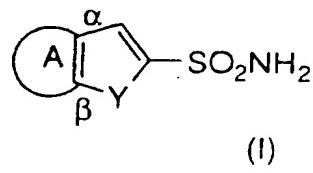
wherein R is selected from -CH<sub>2</sub>CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>1</sup> is selected from CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2</sub>-4 or a pharmaceutically acceptable salt thereof.

19. A method for preventing age-related macular degeneration which comprises applying to the eye an effective amount of a topical carbonic anhydrase inhibitor.

20. The method according to Claim 19 wherein the carbonic anhydrase inhibitor comprises dorzolamide, acetazolamide and methazolamide.

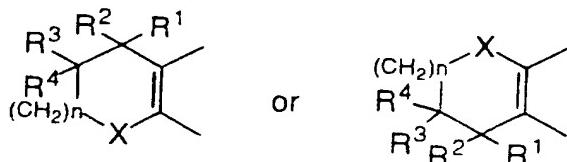
21. The method according to Claim 20 wherein the carbonic anhydrase inhibitor is dorzolamide.

22. The method according to Claim 19 wherein the carbonic anhydrase inhibitor is a compound of the formula



- 32 -

wherein A together with the two carbon atoms denoted as  $\alpha$  and  $\beta$  is the group



wherein:

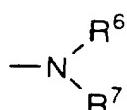
X is -S-, -SO-, -SO<sub>2</sub>- or -CH<sub>2</sub>-;

Y is -S-, -O-, or -NR<sup>3</sup>- wherein R<sup>3</sup> is hydrogen, C<sub>1-3</sub>alkyl, or benzyl;

n is 1 or 2;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently selected from:

- 1) hydrogen,
- 2) OR<sup>5</sup> wherein R<sup>5</sup> is:
  - a) hydrogen,
  - b) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with -OH, or



wherein R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>1-5</sub> alkyl, or joined together form a heterocycle with the nitrogen to which they are attached such as piperidino, morpholino, or

- c) piperazino,
- C<sub>1-5</sub> alkanoyl, either unsubstituted or substituted with -OH, -NR<sup>6</sup>R<sup>7</sup>, -NH-COR<sup>8</sup> or -COR<sup>8</sup> wherein R<sup>8</sup> is -OH, -NR<sup>6</sup>R<sup>7</sup> or C<sub>1-5</sub> alkoxy,

- 33 -

- d) -CO-R<sup>9</sup>, wherein R<sup>9</sup> is -NR<sup>6</sup>R<sup>7</sup> or a 5- or 6-membered aromatic heterocycle such as pyridyl, imidazolyl, pyrazinyl, thiazolyl, thienyl, or oxazolyl,
- 3) -NR<sup>6</sup>R<sup>7</sup>,
- 4) -NHR<sup>10</sup> wherein R<sup>10</sup> is:
  - a) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>,
  - b) -SO<sub>2</sub>R<sup>11</sup>, wherein R<sup>11</sup> is C<sub>1-5</sub> alkyl, or
  - c) -CONR<sup>6</sup>R<sup>7</sup>,
- 5) C<sub>1-5</sub> alkyl, either unsubstituted or substituted with
  - a) -OR<sup>5</sup>,
  - b) -CN,
  - c) -NR<sup>6</sup>R<sup>7</sup>, or
  - d) -COR<sup>8</sup>,
- 6) -SO<sub>2</sub>R<sup>11</sup>,
- 7) -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, or
- 8) -halo, such as chloro, bromo or fluoro;

R<sup>1</sup> and R<sup>3</sup>, or R<sup>2</sup> and R<sup>4</sup> taken together represent a double bond;

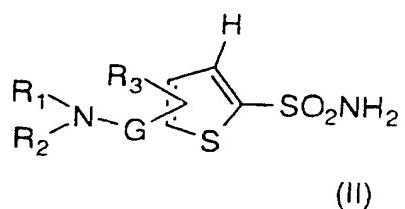
R<sup>1</sup> and R<sup>2</sup>, or R<sup>3</sup> and R<sup>4</sup> taken together represent

- 1) =O, or
- 2) =NOR<sup>12</sup> wherein R<sup>12</sup> is hydrogen or C<sub>1-3</sub>alkyl; and one of the -CH<sub>2</sub>- groups of -(CH<sub>2</sub>)<sub>n</sub>- can be substituted with -COR<sup>8</sup>, -CH<sub>2</sub>R<sup>8</sup>, or -CH<sub>2</sub>COR<sup>8</sup>;

or a pharmaceutically acceptable salt thereof.

- 34 -

23. The method according to Claim 19 wherein the carbonic anhydrase inhibitor is a compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

R<sub>1</sub> is H; C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

R<sub>2</sub> is H; C<sub>1</sub>-8 alkyl; C<sub>2</sub>-8 alkyl substituted with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>3</sub>-7 alkenyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>3</sub>-7 alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>1</sub>-3 alkyl substituted with phenyl or heteroaryl which can be unsubstituted or substituted optionally with OH, C(H<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; C<sub>2</sub>-4 alkoxy substituted optionally with NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, or C(=O)R<sub>7</sub>; phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 haloalkoxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2; provided that R<sub>1</sub> and R<sub>2</sub> cannot both be H; or R<sub>1</sub> and R<sub>2</sub>; can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub> or on nitrogen with NR<sub>5</sub>R<sub>6</sub>, C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl or C<sub>2</sub>-6 alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>.

- 35 -

R<sub>3</sub> is H; halogen; C<sub>1</sub>-4 alkyl; C<sub>1</sub>-8 alkoxy; C<sub>1</sub>-8 alkylthiol; C<sub>2</sub>-8 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkyl substituted optionally with R<sub>4</sub>; or R<sub>1</sub> and R<sub>3</sub> can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R<sub>4</sub>.

R<sub>4</sub> is OH; C<sub>1</sub>-4 alkyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub> halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkoxy; C<sub>2</sub>-4 alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>, NR<sub>5</sub>R<sub>6</sub> phenyl, or heteroaryl, unsubstituted or substituted optionally with OH, (CH<sub>2</sub>)<sub>n</sub>NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1</sub>-4 alkoxy, C<sub>1</sub>-4 haloalkyloxy, C(=O)R<sub>7</sub>, S(=O)<sub>m</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>5</sub>R<sub>6</sub>, wherein m is 0-2 and n is 0-2;

provided that when R<sub>3</sub> is in the 4 position and is H or halogen then R<sub>1</sub> and R<sub>2</sub> are not H, C<sub>1</sub>-6 alkyl substituted optionally with OH, C<sub>1</sub>-6 alkoxy, C<sub>2</sub>-6 alkoxy carbonyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated is substituted optionally with H or C<sub>1</sub>-6 alkyl or in which said carbon is substituted optionally with C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkoxy or OH and when R<sub>3</sub> is in the 5 position and is H, Cl, Br, or C<sub>1</sub>-3 alkyl then neither R<sub>1</sub> nor R<sub>2</sub> can be H or C<sub>1</sub>-4 alkyl.

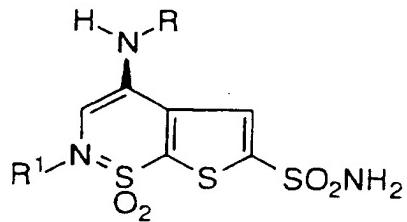
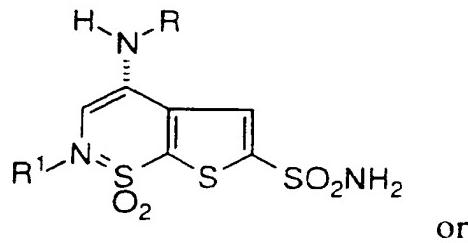
R<sub>5</sub> and R<sub>6</sub> are the same or different and are H; C<sub>1</sub>-4 alkyl; C<sub>2</sub>-4 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>1</sub>-4 alkoxy C<sub>2</sub>-4 alkoxy substituted optionally with OH, halogen; C<sub>1</sub>-4 alkoxy or C(=O)R<sub>7</sub>; C<sub>3</sub>-7 alkenyl unsubstituted or substituted optionally with OH; NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>3</sub>-7 alkynyl unsubstituted or substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, or C<sub>1</sub>-4 alkoxy; C<sub>1</sub>-2 alkyl C<sub>1</sub>-3 cycloalkyl or R<sub>5</sub> and R<sub>6</sub> can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C<sub>1</sub>-4; alkoxy, C(=O)R<sub>7</sub>, C<sub>1</sub>-6 alkyl, C<sub>1</sub>-6 alkyl substituted optionally with OH, halogen, C<sub>1</sub>-4 alkoxy C(=O)R<sub>7</sub> or on nitrogen with C<sub>1</sub>-4 alkoxy, C(=O)R<sub>7</sub>

- 36 -

$S(=O)_m R_8$ , C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkyl substituted optionally with OH, halogen, C<sub>1-4</sub> alkoxy, C(=O)R<sub>7</sub> or on sulfur by (=O)<sub>m</sub> wherein m is 0-2.

- R<sub>7</sub> is C<sub>1-8</sub> alkyl; C<sub>1-8</sub> alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>9</sub>, C<sub>1-4</sub>alkoxy; C<sub>2-4</sub> alkoxy substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen or C<sub>1-4</sub> alkoxy; or NR<sub>5</sub>R<sub>6</sub>.
- R<sub>8</sub> is C<sub>1-4</sub> alkyl; C<sub>2-4</sub> alkyl substituted optionally with OH, NR<sub>5</sub>R<sub>6</sub>, halogen, C<sub>1-4</sub> alkoxy or C(=O)R<sub>7</sub>.
- R<sub>9</sub> is C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkoxy amino, C<sub>1-3</sub> alkylamino, or di-C<sub>1-3</sub> alkylamino; and
- G is C(=O) or SO<sub>2</sub>.

24. The method according to Claim 19 wherein the carbonic anhydrase inhibitor is selected from a compound of the formula



wherein R is selected from -CH<sub>2</sub>CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and R<sup>1</sup> is selected from CH<sub>3</sub>O(CH<sub>2</sub>)<sub>2-4</sub> or a pharmaceutically acceptable salt thereof.

25. The method according to Claim 1 wherein the

- 37 -

carbonic anhydrase inhibitor is administered as a 0.01 to 5% solution in an ophthalmologically acceptable carrier.

26. The method according to Claim 25 wherein the carbonic anhydrase inhibitor is administered as a 0.5 to 2% solution in an ophthalmologically acceptable carrier.

27. The method according to Claim 25 wherein the carbonic anhydrase inhibitor is administered twice daily.

28. The method according to Claim 25 wherein the carbonic anhydrase inhibitor is administered three times daily.



**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/38, 31/54, 31/41</b>	<b>A3</b>	(11) International Publication Number: <b>WO 97/30704</b> (43) International Publication Date: 28 August 1997 (28.08.97)
 <b>(21) International Application Number:</b> PCT/US97/02874 <b>(22) International Filing Date:</b> 25 February 1997 (25.02.97)  <b>(30) Priority Data:</b> 60/012,250 26 February 1996 (26.02.96) US 9605642.9 18 March 1996 (18.03.96) GB		 <b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
 <b>(71) Applicants</b> (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). INDIANA UNIVERSITY FOUNDATION [US/US]; Showalter House, P.O. Box 500, Bloomington, IN 47402 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants</b> (for US only): AMON, Felix, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HARRIS, Alon [US/US]; Showalter House, P.O. Box 500, Bloomington, IN 47402 (US).  <b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		 <b>(88) Date of publication of the international search report:</b> 25 September 1997 (25.09.97)

**(54) Title:** USE OF CARBONIC ANHYDRASE INHIBITORS FOR TREATING MACULAR EDEMA**(57) Abstract**

There is disclosed a method for treating and/or preventing macular edema and age-related macular degeneration which comprises topical administration of carbonic anhydrase inhibitors to the eye.

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## INTERNATIONAL SEARCH REPORT

Intern: Application No  
PCT/US 97/02874

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/38 A61K31/54 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ARCHIVES OF OPHTHALMOLOGY, vol. 106, no. 9, September 1988, USA, pages 1190-1195, XP000197574 S N. COX ET AL: "Treatment of Chronic Macular Edema with Acetazolamide" cited in the application see abstract see page 1191, left-hand column, line 20 - line 23 --- US 4 797 413 A (J. J. BALDWIN ET AL) 10 January 1989 cited in the application see claims 1-13 --- -/-	1-28
Y		1,2,5-8, 11-16, 19-22, 25-28

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

3

Date of the actual completion of the international search  28 July 1997	Date of mailing of the international search report  14.08.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer  Siatou, E

## INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 97/02874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 153 192 A (T. R. DEAN ET AL) 6 October 1992 cited in the application see claims 1-11 see tables 1,2 ---	3,4,9, 10,17, 18,23,24
Y	ARCHIVES OF OPHTHALMOLOGY, vol. 108, no. 11, November 1990, USA, pages 1524-1525, XP000197573 M. F. MARMOR: "Hypothesis Concerning Carbonic Anhydrase Treatment of Cystoid Macular Edema: Example with Epiretinal Membrane" see the whole document ---	1-28
A	GB 2 223 166 A (AMERICAN CYANAMID CO) 4 April 1990 see claims 1-17 see page 7, line 1 - line 12 ---	1-28
A	OPHTHALMIC SURGERY, vol. 25, no. 3, March 1994, USA, pages 166-169, XP000197566 HESAMODIN BORHANI ET AL: "Vitreoretinal Toxicity of Acetazolamide Following Intravitreal Administration in the Rabbit Eye" see abstract ---	1-28
A	KLINISCHE MONATSBLÄTTER FÜR AUGENHEILKUNDE, vol. 202, January 1993, pages 206-211, XP000197567 H. SCHILLING ET AL: "Therapie zystoider und diffuser Makulaödeme nach Uveitis und Katarakt-Chirurgie mit dem Carboanhydrase-Hemmer Acetazolamid (Diamox)" see abstract -----	1-28

# INTERNATIONAL SEARCH REPORT

I national application No.

PCT/US 97/02874

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 1-28 because they relate to subject matter not required to be searched by this Authority, namely:  
Claims 1-28 refer to a method of treatment of the human body and as such as are excluded from patentability. The corresponding use of these compounds was searched.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US/97/02874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4797413 A	10-01-89	US 4677115 A AU 616664 B AU 1838788 A BG 60887 B CA 1328262 A CA 1329211 A CY 1772 A DE 3879292 A EP 0296879 A ES 2053738 T IE 62255 B JP 1100174 A JP 6031247 B KR 9604534 B LU 88633 A SG 24394 A US 4863922 A US 4824968 A	30-06-87 07-11-91 05-01-89 31-05-96 05-04-94 03-05-94 20-10-95 22-04-93 28-12-88 01-08-94 11-01-95 18-04-89 27-04-94 06-04-96 01-09-95 10-06-94 05-09-89 25-04-89
US 5153192 A	06-10-92	AU 655924 B AU 7746791 A CA 2080223 A EP 0527801 A FI 963424 A JP 2562394 B US 5378703 A WO 9115486 A US 5585377 A US 5240923 A	19-01-95 30-10-91 10-10-91 24-02-93 02-09-96 11-12-96 03-01-95 17-10-91 17-12-96 31-08-93
GB 2223166 A	04-04-90	NONE	